## REMARKS

Claims 1, 2, 17, 19, 24, 26-28, 34 and 35 stand rejected, claims 3, 6-9, 14-16, and 25 are objected to, and claims 4, 5, 10-13, 18, 20-23, 29, 32 and 33 are withdrawn. Claim 1 is amended herein to recite that the at least one non-bifunctional oligonucleotide lacks either or both of said first and second separation tags, and that cleavage of a separation tag at the 3' end yields an oligonucleotide having a 3' hydroxyl moiety. Support for this amendment can be found throughout Applicant's specification, including, for example, at page 5, lines 8-9, which state that "non-bifunctional" refers to any oligonucleotide that does not contain both separation tags. Claim 26, which depends from claim 1, is amended herein to recite eluting a non-bifunctional oligonucleotide from step (a), now lacking both the first and second separation tags. Claim 34, which depends from claim 26, is similarly amended to recite eluting a bifunctional oligonucleotide from step (a), now lacking both the first and second separation tags. Support for these amendments can be found in Applicant's specification at, for example, page 17, line 18 to page 18, line 12, which describes a method for separating bifunctional oligonucleotides from non-bifunctional oligonucleotides.

Step (a) of claim 27 is amended to recite that the at least one non-bifunctional oligonucleotide lacks either or both of the first and second separation tags, that the first separation tag interacts more strongly than the second separation tag with the separation medium, and that cleavage of a separation tag at the 3' end yields an oligonucleotide having a 3' hydroxyl moiety. Step (b) of claim 27 is amended to recite contacting the plurality of oligonucleotides with a separation medium under conditions effective for adhering a bifunctional oligonucleotide and a non-bifunctional oligonucleotide lacking the first separation tag to the separation medium. In addition, step (e) of claim 27 is amended to recite eluting non-bifunctional oligonucleotides from step (a), if any, lacking the second separation tag and now also lacking the first separation tag as a result of the cleaving. Support for these amendments can be found in Applicant's specification at, for example, page 11, lines 16-29, which disclose that a mixture of bifunctional and non-bifunctional oligonucleotides can be contacted with a separation medium that retains bifunctional oligonucleotides as well as non-bifunctional oligonucleotides containing the

separation tag that interacts more strongly with the separation medium, and at page 17, line 18 to page 18, line 12, as described above. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1-3, 6-9, 14-17, 19, 24-28, 34 and 35. Applicant further requests rejoinder and allowance of claims 4, 5, 10-13, 18, 20-23, 29, 32 and 33.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 26-28, 34, and 35 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. With respect to claim 26, the Examiner asserted that since step (d) requires only cleaving either the first or second separation tag, it is unclear how to elute an oligonucleotide lacking the first separation tag and an oligonucleotide lacking the second separation tag at the same time as recited in step (e). The Examiner further stated that Applicant's previous response was not persuasive because claims 1 and 26 "do not require that non-bifunctional oligonucleotides have one separation tag and claim 26 does not limit that an oligonucleotide lacking said first separation tag and an oligonucleotide lacking said second separation tag are from a non-bifunctional oligonucleotide."

With respect to claim 27, the Examiner asserted that since step (a) does not require that non-bifunctional oligonucleotides lack the first separation tag or the second separation tag, it is not clear how to elute non-bifunctional oligonucleotides lacking the first separation tag as recited in step (c) or how to elute non-bifunctional oligonucleotides lacking the second separation tag in step (e). With respect to claim 34, the Examiner asserted that there is insufficient antecedent basis for the term "the oligonucleotide" because the word "oligonucleotide" is not recited in step (f).

Applicant disagrees with these rejections. The previous claims were clear and definite, as discussed in Applicant's previous responses. For example, with respect to previous claim 26, a person of skill in the art would have understood that cleavage of either the first separation tag or the second separation tag in step (d) would result in oligonucleotides having one separation tag remaining (i.e., those oligonucleotides that had started out as bifunctional in step (a)), as well as oligonucleotides having no separation tags remaining (i.e., those that had started out in step (a) as

non-bifunctional oligonucleotides having only the separation tag that was cleaved in step (d)). A person of skill in the art also would have appreciated that the oligonucleotides having no separation tags remaining after step (d) would have been those that were eluted in step (e). Thus, previous claim 26 was definite. In addition, for at least the reasons presented in Applicant's previous responses, previous claims 27 and 34 also were definite.

To further prosecution, however, Applicant has amended step (a) of claim 1 to recite that the at least one non-bifunctional oligonucleotide lacks either or both of said first and second separation tags, and has amended claim 26 to recite that step (e) includes eluting a non-bifunctional oligonucleotide from step (a), now lacking the first separation tag and the second separation tag. Thus, it is clear that the non-bifunctional oligonucleotide in claim 1 lacks one or both separation tags, and that the oligonucleotide eluted in step (e) of claim 26 is a non-bifunctional oligonucleotide that now lacks both separation tags. As such, present claim 26 is clear and definite.

Applicant also has amended claim 27 such that step (a) recites that the at least one non-bifunctional oligonucleotide lacks either or both of the first and second separation tags, step (b) recites contacting the plurality of oligonucleotides with a separation medium under conditions effective for adhering a bifunctional oligonucleotide and a non-bifunctional oligonucleotide lacking the first separation tag to the separation medium, and step (e) recites eluting non-bifunctional oligonucleotides from step (a), if any, lacking the second separation tag and now also lacking the first separation tag as a result of the cleaving. A person of skill in the art reading present claim 27 would have understood that the at least one non-bifunctional oligonucleotide lacks one or both separation tags, and that the oligonucleotides eluted in step (c) are non-bifunctional oligonucleotides from step (a), if any, that lacked the first separation tag. A person of skill also would have understood that the oligonucleotides eluted in step (e) are non-bifunctional oligonucleotides that were originally adhered to the separation medium only via the first separation tag, and that are unable to adhere to the medium after cleavage of the first separation tag. As such, claim 27 is clear and definite.

Claim 34 has been amended to recite eluting a bifunctional oligonucleotide from step (a) (of claim 1), now lacking both the first and second separation tags. Thus, amended claim 34 does not include the term "the oligonucleotide," and the rejection of this claim is moot.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 26-28, 34, and 35 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 2, 14, 17, 19, and 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by the Bonora *et al.* reference (*Nucl. Acids Res.* 18:3155-3159, 1990). The Examiner alleged, *inter alia*, that the Bonora *et al.* reference discloses a method for separating oligonucleotides that includes:

> . . . providing a plurality of oligonucleotides (i.e., crude synthesized oligonucleotides) comprising at least one bifunctional oligonucleotide . . . wherein each said at least one bifunctional oligonucleotide comprises a first separation tag (i.e., phosphate group at the 5' end or hydroxyl group at the 3' end) attached to a first end of said at least one bifunctional oligonucleotide and a second separation tag (i.e., phosphate group at the 5' end or hydroxyl group at the 3' end) attached to a second end of said at least one bifunctional oligonucleotide . . .

Applicant respectfully disagrees. To anticipate a claim, a reference must teach every element of the claim. M.P.E.P. § 2131. The Bonora *et al.* reference does not teach every element of independent claim 1, and thus fails to anticipate the present claims. This is particularly true given that at no point does the Bonora *et al.* reference disclose a bifunctional oligonucleotide as recited in the present claims, i.e., an oligonucleotide having a separation tag at each end. Applicant's specification teaches that the term "separation tag" refers to a chemical group or moiety bonded to either the 3' or 5' end of an oligonucleotide that allows an oligonucleotide having the separation tag to be separated from other oligonucleotides that lack this function. Suitable separation tags for the 5' end of the oligonucleotide are disclosed to include those that provide a separation function in addition to protecting the terminal hydroxyl residue, and are said to include known hydrophobic groups such as dimethoxytrityl (DMTr), pixyl, alkoxytrityl, and alkoxypixyl protecting groups, including octadecyloxypixyl phynylxanthyl (C18Px), 4-decyloxymethoxy trityl (C10Tr), 4 hexyloxymethoxytrityl (C6Tr), and monomethoxytrityl (MMTr) groups, as well as hydrocarbon chains introduced in a form of a linear or branched diol, alkyldithioformacetal, methylthioalkyl and derivatives of mercaptodimethoxytrityl or mercaptotrityl. *See*, e.g., page 7, lines 23-25 and page 8, lines 3-8.

Thus, it is clear from Applicant's specification that a phosphate group at the 5' end is not considered a separation tag.

Further, Applicant's specification discloses that a separation tag on the 3' end of an oligonucleotide can be a component of the linker between the solid support and the first nucleotide (i.e., the 3' end of the oligonucleotide), and that 3' separation tags typically are stable under treatment in aqueous ammonia so they are not cleaved from the oligonucleotide when the oligonucleotide is released from the solid support. The specification also discloses that a cleavable unit of a 3' separation tag can be attached to the 3' oxygen of the first nucleotide in the oligomer, that suitable cleavable units on the 3' end of an oligonucleotide regenerate a free 3' OH after being cleaved, and that disiloxyl groups, alkyl thiomethyl and hydrocarbyldithiomethyl groups, photolabile groups, redox active groups, and electrophilic reagents are examples of suitable cleavable units that can be components of a linker. *See*, page 6, line 18 to page 7, line 7. Thus, it is clear from Applicant's specification that a hydroxyl group at the 3' end is not considered a separation tag.

Moreover, present claim 1 recites that cleavage of a separation tag at the 3' end yields an oligonucleotide having a 3' hydroxyl moiety. According to the Examiner's scenario, a hydroxyl group is useful as a 3' separation function. Applicant notes, however, that not only is a 3' hydroxyl group unsuitable as a 3' separation function as discussed above, but cleavage of a 3' hydroxyl group would not yield an oligonucleotide having a 3' hydroxyl moiety. Thus, the Examiner's assertions that a hydroxyl group present on an oligonucleotide is equivalent to a separation tag are incorrect.

Given the above, it is clear that the Bonora *et al.* reference discloses neither a bifunctional oligonucleotide having 5' and 3' separation functions, nor a separation tag that would result in a 3' hydroxyl moiety upon cleavage, as recited in the present claims. Thus, for at least these reasons, the Bonora *et al.* reference fails to anticipate the presently claimed methods.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 14, 17, 19, and 24 under 35 U.S.C. § 102(b).

The Examiner rejected claims 1, 7-9, 14, 17, 19, and 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,997,927 (the Blocker *et al.* patent). The Examiner alleged, *inter alia*, that the Blocker *et al.* patent discloses a method that includes:

> . . . providing a plurality of oligonucleotides (i.e., crude synthesized oligonucleotides) comprising at least one bifunctional oligonucleotide . . . wherein each said at least one bifunctional oligonucleotide comprises a first separation tag (i.e., trityl group at the 5' end or hydroxyl group at the 3' end) attached to a first end of said at least one bifunctional oligonucleotide and a second separation tag (i.e., trityl group at the 5' end or hydroxyl group at the 3' end) attached to a second end of said at least one bifunctional oligonucleotide . . .

Applicant respectfully disagrees. The Blocker *et al.* patent does not disclose all elements of independent claim 1, and thus does not anticipate the present claims. For example, like the Bonora *et al.* reference, the Blocker *et al.* patent fails to disclose bifunctional nucleotides as recited in the present claims. Again, Applicant's specification discloses that a separation tag is a chemical group or moiety bonded to either the 3' or 5' end of an oligonucleotide that allows an oligonucleotide having the separation tag to be separated from other oligonucleotides that lack the separation tag, that a cleavable unit of a 3' separation tag can be attached to the 3' oxygen of the first nucleotide in the oligomer, that suitable cleavable units on the 3' end of an oligonucleotide regenerate a free 3' OH after being cleaved, and that disiloxyl groups, alkyl thiomethyl and hydrocarbyldithiomethyl groups, photolabile groups, redox active groups, and electrophilic reagents are examples of suitable cleavable units that can be components of a linker. Thus, it is clear that a hydroxyl group at the 3' end is not considered a separation tag. Further, present claim 1 recites that cleavage of either the first separation tag or the second separation tag yields an oligonucleotide having a 3' hydroxyl moiety. It is clear that cleavage of a 3' hydroxyl group would not yield an oligonucleotide having a 3' hydroxyl moiety. Thus, the Examiner's assertions that a hydroxyl group at the 3' of an oligonucleotide is equivalent to a separation tag are incorrect. For at least these reasons, the Blocker *et al.* patent does not anticipate the present claims.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 7-9, 14, 17, 19, and 24 under 35 U.S.C. § 102(b).

Claim objections

Applicant acknowledges the Examiner's objection to claims 3, 6-9, 14-16, and 25. In light of the amendments and remarks presented herein, Applicant has not amended these claims to be in independent form or to otherwise recite all limitations of the independent claims.

Request for rejoinder of withdrawn claims

In the Response to Restriction Requirement mailed August 6, 2004, Applicant made several species elections that resulted in claims being withdrawn. Given the allowability of claims cited by the Examiner as being generic to the distinct species, Applicant respectfully requests consideration of claims to additional species as provided by 37 C.F.R. § 1.141. (*See*, M.P.E.P. § 809.02(a). *See, also*, M.P.E.P. § 818.03(d), which states that if the Office allows a linking claim, it is bound to withdraw the requirement and to act on all linked inventions.) Thus, Applicant requests rejoinder of the withdrawn claims as follows:

First, the Examiner stated that claim 1 is generic to claims 3-6. Claims 4 and 5 were withdrawn. Since claims 4 and 5 depend directly or indirectly from claim 1, which is in condition for allowance, Applicant respectfully requests rejoinder of claims 4 and 5.

Second, the Examiner stated that claim 1 is generic to claims 8-13. Claims 10-13 were withdrawn. Since claims 10-13 depend indirectly from claim 1, which has been allowed, Applicant respectfully requests rejoinder of claims 10-13.

Third, the Examiner stated that claim 1 is generic to claims 17-23. Claims 18 and 20-23 were withdrawn. Since claims 20-23 depend directly or indirectly from claim 1, which is in condition for allowance, Applicant respectfully requests rejoinder of claims 18 and 20-23.

Fourth, the Examiner stated that claim 27 is generic to claims 28-29. Claim 29 was withdrawn. Since claim 29 depends directly from claim 27, which is in condition for allowance, Applicant respectfully requests rejoinder of claim 29.

Finally, the Examiner stated that claim 1 is generic to claims 16, 32, and 33. Claims 32 and 33 were withdrawn. Since claims 32 and 33 depend directly from claim 1, which is in condition for allowance, Applicant respectfully requests rejoinder of claims 32 and 33.

## CONCLUSION

Applicant submits that claims 1-3, 6-9, 14-17, 19, 24-28, 34, and 35 are in condition for allowance, which action is respectfully requested. Applicant also requests rejoinder and allowance of claims 4, 5, 10-13, 18, 20-23, 29, 32, and 33. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $510 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: July 18, 2007

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